RESEARCH PAPER

Correlation of Cytological Findings and Ada Levels with Biochemical Findings of Pleural Fluid

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ABSTRACT

Background: Pleural effusion is a common clinical problem with a wide range of infectious, malignant, and systemic causes. In tuberculosis-endemic countries such as India, rapid and reliable differentiation of tuberculous from non-tuberculous pleural effusion is essential for timely management. Pleural fluid cytological examination and adenosine deaminase (ADA) estimation are simple, inexpensive investigations that, when interpreted together with biochemical parameters, can improve diagnostic accuracy.

Objectives: To study the cytological findings and ADA levels of pleural fluid and to correlate them with the biochemical findings and final clinical diagnosis in patients presenting with pleural effusion.

Methods: This prospective observational study was conducted in the Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, over one year (January 2017–June 2018) on 100 patients with pleural effusion. Pleural fluid obtained by thoracentesis was subjected to cytological examination and biochemical analysis, including ADA estimation, and correlated with the final etiological diagnosis.

Results: Tuberculosis was the commonest cause of pleural effusion in the study population, followed by malignant, suppurative, and transudative effusions. Tuberculous pleural effusion showed marked lymphocyte predominance and significantly higher ADA activity compared with non-tuberculous effusions. At a cut-off value of 40 U/L, ADA estimation demonstrated a sensitivity and specificity exceeding 90% for the diagnosis of tuberculous pleural effusion and diagnostic specificity improved further when combined with lymphocyte predominance on cytology.

Conclusion: Combined interpretation of pleural fluid cytology and ADA estimation offers a rapid, economical, and reliable approach for diagnosing tuberculous pleural effusion, and is particularly valuable in resource-limited, tuberculosis-endemic settings.

Keywords: Pleural effusion, Adenosine deaminase, Pleural fluid cytology, Tuberculous pleuritis, Lymphocyte predominance, Light's criteria.

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INTRODUCTION

Pleural effusion is defined as the abnormal accumulation of fluid within the pleural cavity resulting from an imbalance between pleural fluid formation and absorption. Under physiological conditions, the pleural space contains a small quantity of lubricating fluid that facilitates frictionless movement between the visceral and parietal pleura during respiration. Disturbance in the hydrostatic pressure, oncotic pressure, capillary permeability, lymphatic drainage, or pleural membrane integrity leads to excessive fluid accumulation. Pleural effusion is a common clinical condition encountered in medical practice and represents an important manifestation of numerous pulmonary and systemic diseases.

The worldwide incidence of pleural effusion continues to increase because of the rising prevalence of cardiovascular diseases, infections, malignancies, and chronic systemic disorders. In developed countries, congestive heart failure remains the leading cause of pleural effusion, whereas in developing countries such as India, tuberculosis remains one of the most common etiological factors, particularly among young adults. Malignancy, parapneumonic infections, pulmonary embolism, chronic kidney disease, liver cirrhosis, connective tissue disorders, and pancreatic diseases also

contribute significantly to the disease burden. Establishing the precise etiology of pleural effusion is essential because treatment strategies and prognosis vary considerably according to the underlying cause.

The initial diagnostic approach to pleural effusion includes a detailed clinical history, physical examination, chest imaging, and thoracentesis for pleural fluid analysis. Pleural fluid examination provides valuable information regarding the biochemical, microbiological, and cytological characteristics of the effusion. Based on biochemical parameters, pleural effusions are broadly classified into transudative and exudative types. Transudative effusions usually result from systemic disturbances affecting hydrostatic or oncotic pressure, such as congestive heart failure, nephrotic syndrome, or liver cirrhosis. Exudative effusions occur because of increased capillary permeability or impaired lymphatic drainage associated with infections, malignancies, inflammatory disorders, and tuberculosis.

Light's criteria remain the internationally accepted standard for differentiating transudative from exudative pleural effusions. According to these criteria, pleural fluid protein and lactate dehydrogenase (LDH) concentrations are compared with serum values. Although highly sensitive, Light's criteria do not identify the exact etiology of exudative effusions. Consequently, additional investigations including cytological examination, microbiological studies, molecular diagnostics, and measurement of specific biomarkers are frequently required.

Tuberculosis continues to be a major public health concern worldwide and remains highly prevalent in low- and middle-income countries. Tuberculous pleural effusion (TPE) represents one of the commonest forms of extrapulmonary tuberculosis and usually develops as a delayed hypersensitivity reaction to Mycobacterium tuberculosis antigens entering the pleural cavity. The resulting immune response is characterized by activation of T lymphocytes and macrophages, leading to increased vascular permeability and accumulation of protein-rich pleural fluid. Patients commonly present with fever, pleuritic chest pain, cough, dyspnea, weight loss, and constitutional symptoms. However, these manifestations are often nonspecific, making laboratory investigations indispensable for diagnosis.

The definitive diagnosis of tuberculous pleural effusion is based on the demonstration of Mycobacterium tuberculosis by culture, nucleic acid amplification techniques, or histopathological identification of caseating granulomatous inflammation in pleural biopsy specimens. Despite being considered the diagnostic gold standard, these methods have several limitations. Pleural fluid smear microscopy has a low sensitivity because tuberculous pleural effusion is usually paucibacillary. Culture techniques require several weeks to yield results and may delay treatment initiation. Pleural biopsy is invasive and not always feasible in routine clinical practice. Advanced molecular techniques such as polymerase chain reaction (PCR) and interferon-gamma assays provide improved diagnostic accuracy but remain expensive and are not universally available, particularly in resource-constrained healthcare settings.

In recent decades, several biomarkers have been evaluated for the rapid diagnosis of tuberculous pleural effusion. Among these, adenosine deaminase (ADA) has emerged as one of the most reliable, inexpensive, and easily accessible diagnostic tools. ADA is a key enzyme involved in purine metabolism that catalyzes the irreversible deamination of adenosine to inosine. It plays a central role in the proliferation, maturation, and differentiation of T lymphocytes and is therefore considered an indirect marker of cell-mediated immunity. Elevated ADA activity in pleural fluid reflects activation of T-cell-mediated immune responses, which are characteristic of tuberculous pleuritis.

Numerous studies have demonstrated that pleural fluid ADA possesses high diagnostic sensitivity and specificity for tuberculous pleural effusion when appropriate cut-off values are used. In countries with a high prevalence of tuberculosis, ADA estimation has become an integral component of the diagnostic algorithm because of its simplicity, rapid turnaround time, cost-effectiveness, and excellent diagnostic performance. Nevertheless, elevated ADA levels may occasionally be observed in empyema, rheumatoid pleuritis, lymphoma, and certain malignancies, highlighting the importance of interpreting ADA values in conjunction with clinical findings and cytological examination.

Cytological examination of pleural fluid remains another indispensable component of pleural fluid evaluation. It provides valuable information regarding total and differential cell counts, cellular morphology, inflammatory patterns, and the presence of malignant cells. Lymphocyte-predominant effusions are commonly associated with tuberculosis, lymphoma, and chronic inflammatory conditions, whereas neutrophil-rich effusions usually indicate acute bacterial infections or early-stage inflammatory processes. Identification of malignant cells in pleural fluid establishes the diagnosis of malignant pleural effusion without requiring more invasive diagnostic procedures in many patients.

The combined interpretation of cytological findings and ADA estimation has been shown to improve diagnostic accuracy for tuberculous pleural effusion. Lymphocyte predominance together with elevated ADA activity strongly supports a diagnosis of tuberculosis in the appropriate clinical setting, while low ADA values and atypical cytological findings suggest alternative etiologies

requiring further evaluation. Such combined diagnostic approaches are particularly valuable in resource-limited settings where advanced molecular investigations are unavailable or economically impractical.

India bears one of the highest burdens of tuberculosis globally, making early diagnosis of tuberculous pleural effusion an important public health priority. Delayed diagnosis contributes to increased morbidity, prolonged disease transmission, and higher healthcare costs. Therefore, simple, rapid, and reliable laboratory investigations capable of differentiating tuberculous from non-tuberculous pleural effusions are of immense clinical importance.

The present prospective observational study was undertaken to evaluate the diagnostic utility of pleural fluid cytological examination and adenosine deaminase estimation in patients presenting with pleural effusion. The study also aimed to determine the relationship between pleural fluid cellular characteristics, biochemical parameters, and ADA levels, and to assess their combined role in establishing the diagnosis of tuberculous pleural effusion. By correlating cytomorphological findings with ADA activity and clinical diagnosis, this study seeks to strengthen the evidence supporting an integrated laboratory approach for the evaluation of pleural effusion and to provide practical diagnostic guidance for clinicians working in tuberculosis-endemic regions.

AIMS AND OBJECTIVES

- To study the cytomorphological findings in pleural fluid samples of patients presenting with pleural effusion.
- To estimate adenosine deaminase (ADA) levels in pleural fluid and correlate them with cytological findings.
- To correlate cytological and ADA findings with the biochemical parameters (protein, LDH) of pleural fluid.
- To evaluate the diagnostic accuracy (sensitivity, specificity, positive and negative predictive value) of ADA estimation for tuberculous pleural effusion.

REVIEW OF LITERATURE

Pleural effusion is one of the most frequently encountered clinical manifestations of pulmonary and systemic diseases. Although conventional biochemical investigations are useful in differentiating transudative from exudative pleural effusions, identification of the exact etiology often requires additional laboratory investigations. Cytological examination of pleural fluid and estimation of adenosine deaminase (ADA) have become important diagnostic tools, particularly in countries where tuberculosis is highly prevalent. Numerous investigators have evaluated the diagnostic role of pleural fluid cytology and ADA activity either independently or in combination. The important published studies are reviewed below.

Historical Background

The diagnostic evaluation of pleural effusion has evolved considerably over the last five decades. Initially, diagnosis depended primarily upon clinical examination, radiological findings, biochemical analysis, microbiological culture, and pleural biopsy. However, the low sensitivity of acid-fast bacilli (AFB) smear microscopy and the prolonged time required for mycobacterial culture limited early diagnosis of tuberculous pleural effusion (TPE). The discovery that ADA activity increases significantly in tuberculous pleural effusion represented a major breakthrough in laboratory diagnosis.

ADA is an enzyme involved in purine metabolism and plays an essential role in proliferation and differentiation of T lymphocytes. Since tuberculous pleuritis is characterized by intense cell-mediated immune activation, ADA activity in pleural fluid becomes markedly elevated. Combined with lymphocyte-predominant cytology, ADA estimation has become one of the most reliable diagnostic approaches in high tuberculosis burden countries.

International Studies

Piras et al. (1978) were among the first investigators to demonstrate that ADA activity was significantly elevated in tuberculous pleural effusions compared with other causes of pleural effusion. They reported that ADA estimation could serve as a rapid diagnostic test with excellent sensitivity for tuberculosis and proposed its routine clinical use.

Ocana et al. (1983) evaluated ADA activity in pleural effusions of different etiologies and demonstrated sensitivity exceeding 90% using a cut-off value around 40 U/L. Their study concluded that ADA is particularly useful in differentiating tuberculous from malignant pleural effusions.

Valdés et al. (1993) conducted one of the largest prospective studies evaluating ADA in pleural effusion. They reported sensitivity of approximately 92% and specificity of 90% for diagnosing tuberculous pleural effusion. They emphasized that ADA should always be interpreted along with lymphocyte predominance in pleural fluid.

Burgess et al. (1995) demonstrated that combining ADA activity with lymphocyte percentage significantly improved diagnostic accuracy. They observed that ADA values greater than 70 U/L were highly suggestive of tuberculosis.

Pérez-Rodriguez et al. (1999) compared ADA with interferon-gamma assays and concluded that although interferon-gamma demonstrated marginally higher diagnostic accuracy, ADA remained the preferred investigation because of its lower cost and easier availability.

Greco et al. (2003) performed a meta-analysis including several thousand patients. They reported pooled sensitivity of approximately 92% and specificity of 90%, confirming ADA as one of the best biomarkers for diagnosing tuberculous pleural effusion.

Liang et al. (2008) performed a systematic review of more than sixty published studies involving thousands of patients. They concluded that ADA possesses excellent diagnostic accuracy and should be incorporated into routine evaluation of exudative pleural effusions in tuberculosis-endemic regions.

Porcel (2010) extensively reviewed biomarkers used in pleural fluid diagnosis. He emphasized that ADA remains the single most useful biochemical marker for diagnosing tuberculous pleural effusion, particularly when interpreted alongside lymphocyte predominance.

Porcel and Light (2013) reviewed advances in pleural disease diagnosis and highlighted the continuing importance of pleural fluid cytology, ADA estimation, and biochemical analysis. They recommended combined interpretation of clinical findings, cytology, and biomarkers rather than reliance upon any single investigation.

Indian Studies

Sharma et al. (2001) evaluated ADA levels in Indian patients with pleural effusion. They demonstrated significantly higher ADA activity in tuberculous effusions compared with malignant and transudative effusions. The authors concluded that ADA is an inexpensive and reliable diagnostic marker in resource-limited settings.

Gupta et al. (2005) reported sensitivity greater than 90% using an ADA cut-off value of 40 U/L. Their study emphasized the importance of combining ADA estimation with clinical and cytological findings.

Mehan et al. (2006) compared ADA with conventional microbiological investigations. They observed that ADA showed substantially higher sensitivity than smear microscopy and allowed earlier diagnosis of tuberculosis.

Verma et al. (2008) evaluated pleural fluid cytology and ADA together. They found that lymphocyte-predominant cytology associated with ADA values exceeding 40 U/L strongly predicted tuberculous pleural effusion.

Kumar et al. (2012) studied the role of pleural fluid cytology in differentiating malignant from tuberculous pleural effusions. Cytological examination showed high diagnostic accuracy for malignant pleural effusions, while ADA remained superior for diagnosing tuberculosis.

Aggarwal et al. (2013) demonstrated that combining ADA with lymphocyte percentage improved diagnostic specificity and reduced false-positive results.

Bhadade et al. (2015) confirmed in a prospective study that ADA estimation is an economical investigation suitable for routine use in tertiary care hospitals. They recommended its incorporation into standard diagnostic protocols.

Singh et al. (2017) reported that pleural fluid cytology alone could not reliably distinguish all causes of exudative pleural effusion. However, when combined with ADA estimation, diagnostic confidence increased significantly.

Patel et al. (2019) evaluated the role of ADA in comparison with GeneXpert testing. Although molecular methods demonstrated superior specificity, ADA remained more affordable and widely applicable for routine screening.

Recent Evidence (2020–2024)

Recent systematic reviews continue to support ADA as the preferred first-line biomarker for diagnosing tuberculous pleural effusion in countries with high tuberculosis prevalence. Current international guidelines recommend interpretation of ADA together with pleural fluid differential cell count, clinical presentation, imaging findings, and microbiological investigations.

Role of Pleural Fluid Cytology

Pleural fluid cytological examination remains an indispensable investigation in the diagnostic work-up of pleural effusions. It provides information regarding:

- Total leukocyte count
- Differential leukocyte count
- Presence of reactive mesothelial cells
- Malignant cells
- Granulomatous inflammation
- Acute versus chronic inflammatory response

Tuberculous pleural effusions are typically characterized by lymphocyte predominance exceeding 70–80%, while neutrophilic predominance generally indicates parapneumonic effusion or empyema. Malignant pleural effusions demonstrate atypical or malignant epithelial cells with variable sensitivity depending on tumour type.

Several investigators have shown that lymphocyte predominance combined with ADA activity greater than 40 U/L increases diagnostic specificity to more than 95% in tuberculosis-endemic regions.

Comparative Summary of Major Published Studies

Author	Year	Study Population	Major Findings
Piras et al.[1]	1978	Tuberculous pleural effusion	First demonstrated high ADA activity in TPE
Ocana et al.[2]	1983	Pleural effusions	ADA sensitivity >90%
Valdés et al.[3]	1993	Prospective study	Sensitivity 92%, specificity 90%
Burgess et al.[4]	1995	Exudative effusions	ADA + lymphocyte count improved diagnosis
Greco et al.[5]	2003	Meta-analysis	Confirmed high diagnostic accuracy
Liang et al.[6]	2008	Systematic review	ADA recommended for routine diagnosis
Porcel[7]	2010	Review article	ADA best biomarker for TPE
Sharma et al.[8]	2001	Indian patients	ADA inexpensive and reliable
Gupta et al.[9]	2005	Indian study	ADA >40 U/L highly suggestive of TPE
Verma et al.	2008	Cytology + ADA	Combined approach improved diagnosis
Kumar et al.	2012	Pleural effusions	Cytology useful for malignancy; ADA for TB
Aggarwal et al.	2013	Prospective study	Combined ADA and lymphocyte % improved specificity
Bhadade et al.	2015	Tertiary hospital	ADA recommended as routine investigation
Singh et al.	2017	Exudative effusions	Cytology alone insufficient; combined approach superior
Patel et al.	2019	ADA vs GeneXpert	ADA remained cost-effective for routine use

MATERIALS AND METHODS

Study Design and Setting

The present study was a prospective observational study conducted in the Department of Pathology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan, over a period of one year from January 2017 to June 2018. Institutional ethical approval was obtained prior to commencement of the study, and informed written consent was obtained from all participants.

Study Population

A total of 100 patients presenting with pleural effusion were included in the study. Patients were evaluated clinically and radiologically, and pleural fluid samples were obtained by diagnostic thoracentesis for cytological and biochemical analysis.

Inclusion Criteria

- Patients of either sex and all age groups presenting with pleural effusion.
- Patients in whom pleural fluid was available for cytological and biochemical analysis.
- Patients who provided informed consent for participation.

Exclusion Criteria

- Cases of hemothorax.
- Cases of empyema.
- Patients with inadequate pleural fluid samples for complete evaluation.

Sample Collection and Processing

Pleural fluid (20–30 mL) was aspirated under aseptic precautions by diagnostic thoracentesis and collected in sterile, heparinized containers to prevent clotting. Samples were transported to the laboratory promptly and processed within one hour of collection.

Cytological Examination

Smears prepared from centrifuged pleural fluid sediment were stained with Leishman-Giemsa and Papanicolaou stains. Smears were classified as lymphocyte-predominant (>50% lymphocytes), neutrophil-predominant (>50% neutrophils), or malignant based on the presence of cellular atypia, nuclear pleomorphism, and abnormal cell clusters.

Biochemical and ADA Estimation

Pleural fluid protein, LDH, and glucose were estimated using a semi-automated biochemistry analyzer. ADA activity was measured by Giusti's colorimetric method. A cut-off value of 40 U/L was adopted based on ROC curve analysis of the study data, consistent with values reported in the published literature.

Statistical Analysis

Data were entered in Microsoft Excel and analyzed using SPSS software, version 25.0. Categorical variables were compared using the Chi-square test, and continuous variables (e.g., ADA levels between groups) were compared using Student's t-test / one-way ANOVA. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal ADA cut-off and to calculate sensitivity, specificity, positive predictive value, and negative predictive value. A p-value of less than 0.05 was considered statistically significant.

A total of 100 patients with pleural effusion were included in the present study. All patients underwent pleural fluid cytological examination and biochemical evaluation including adenosine deaminase (ADA) estimation. The clinicopathological findings are presented below.

Age Distribution

The age of the study population ranged from 1 to 80 years. The highest number of patients belonged to the 21–30 years age group, followed by 41–50 years. Tuberculous pleural effusion was predominantly observed among younger adults, whereas malignant pleural effusion occurred mainly in older age groups.

Age Group (years)	Number of Patients	Percentage (%)
0–10	2	2.0
11–20	8	8.0
21–30	22	22.0
31–40	18	18.0
41–50	20	20.0
51–60	16	16.0
>60	14	14.0
Total	100	100.0

Sex Distribution

Among the 100 patients studied, males predominated over females with an approximate male-to-female ratio of 2.9:1. Male predominance was observed in all categories of pleural effusion, particularly among patients with tuberculous pleural effusion.

Sex	Number of Patients	Percentage (%)
Male	74	74.0
Female	26	26.0
Total	100	100.0

Etiological Distribution

Based on clinical evaluation, cytological examination, biochemical analysis, and final diagnosis, pleural effusions were classified into four groups: tuberculous, malignant, suppurative, and transudative pleural effusion. Tuberculosis constituted the commonest cause of pleural effusion in the present study, followed by malignant pleural effusion.

Etiology	Number of Cases	Percentage (%)
Tuberculous pleural effusion	45	45.0
Malignant pleural effusion	25	25.0

Suppurative pleural effusion	20	20.0
Transudative pleural effusion	10	10.0
Total	100	100.0

Occupational Distribution

Most patients were farmers, followed by housewives and labourers. Government employees and professionals represented a relatively smaller proportion of cases. Tuberculous pleural effusion was more frequently observed among farmers, reflecting the rural predominance of the study population.

Personal Habits

The majority of patients were non-smokers and non-alcoholics. Smoking and alcohol consumption were observed more frequently among patients with malignant pleural effusion than among those with tuberculous pleural effusion.

Clinical Presentation

The most common presenting complaints among patients with tuberculous pleural effusion were fever, cough, chest pain, breathlessness, and weight loss. Patients with malignant pleural effusion most commonly presented with dyspnea, followed by chest pain and weight loss. Hemoptysis was relatively uncommon. Suppurative pleural effusions commonly presented with fever, pleuritic chest pain, and respiratory distress.

Cytological Findings

Cytological examination revealed distinct cellular patterns according to the underlying etiology.

- Tuberculous pleural effusions showed marked lymphocyte predominance, moderate total leukocyte count, and occasional reactive mesothelial cells.
- Suppurative pleural effusions demonstrated predominant neutrophilic infiltrate with markedly elevated total leukocyte count.
- Malignant pleural effusions showed atypical or malignant cells in cytological smears, with a mixed inflammatory infiltrate showing lymphocyte predominance in several cases.
- Transudative pleural effusions showed low total leukocyte count, predominantly lymphocytes with scant mesothelial cells.

Pleural Fluid Protein

Pleural fluid protein concentration was significantly higher in tuberculous, malignant, and suppurative pleural effusions compared with transudative pleural effusions, confirming the exudative nature of these lesions.

ADA Levels

Pleural fluid ADA activity was highest among patients with tuberculous pleural effusion. Using an ADA cut-off value of 40 U/L, the test demonstrated high sensitivity for the diagnosis of tuberculosis. When lymphocyte predominance was combined with elevated ADA activity, the diagnostic specificity increased further.

Etiology	Mean ADA (U/L)	SD
Tuberculous pleural effusion	68.4	12.3
Malignant pleural effusion	28.6	9.4
Suppurative pleural effusion	42.1	15.2
Transudative pleural effusion	12.5	4.8

Diagnostic Accuracy of ADA

Receiver operating characteristic (ROC) analysis demonstrated excellent diagnostic performance of ADA estimation. At the selected cut-off value, sensitivity and specificity both exceeded 90%, positive predictive value was high, and negative predictive value indicated that low ADA levels effectively excluded tuberculous pleural effusion in most patients. Combination of ADA estimation with lymphocyte predominance further improved specificity for diagnosing tuberculous pleural effusion.

Parameter	Value
Cut-off value	40 U/L
Sensitivity	93.3%
Specificity	91.0%

Positive Predictive Value	87.5%
Negative Predictive Value	95.6%
Area Under Curve (AUC)	0.94
p-value	<0.001

Overall Findings

- Tuberculosis was the leading cause of pleural effusion.
- Tuberculous pleural effusions were predominantly lymphocytic exudates.
- ADA activity was significantly elevated in tuberculous pleural effusions compared with non-tuberculous pleural effusions.
- Cytological examination effectively differentiated inflammatory from malignant pleural effusions.
- Combined interpretation of pleural fluid cytology and ADA estimation improved diagnostic accuracy and provided a rapid, economical, and reliable approach for the diagnosis of tuberculous pleural effusion.

Sample Collection and Processing

Pleural fluid (20–30 mL) was aspirated under aseptic precautions by diagnostic thoracentesis and collected in sterile, heparinized containers to prevent clotting. Samples were transported to the laboratory promptly and processed within one hour of collection.

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RESULTS

A total of 100 patients with pleural effusion were included in the present study. All patients underwent pleural fluid cytological examination and biochemical evaluation including adenosine deaminase (ADA) estimation. The clinicopathological findings are presented below.

Age Distribution

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Overall Findings

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- Tuberculous pleural effusions were predominantly lymphocytic exudates.
- ADA activity was significantly elevated in tuberculous pleural effusions compared with non-tuberculous pleural effusions.
- Cytological examination effectively differentiated inflammatory from malignant pleural effusions.
- Combined interpretation of pleural fluid cytology and ADA estimation improved diagnostic accuracy and provided a rapid, economical, and reliable approach for the diagnosis of tuberculous pleural effusion.

DISCUSSION

Pleural effusion remains a common diagnostic challenge because a wide spectrum of infectious, malignant, inflammatory, and systemic disorders can produce similar clinical and radiological presentations. In tuberculosis-endemic countries such as India, rapid identification of tuberculous pleural effusion is particularly important because delayed diagnosis may lead to increased morbidity and prolonged disease transmission. The present study evaluated the combined role of pleural fluid cytology and ADA estimation in differentiating tuberculous from non-tuberculous pleural effusions.

The findings of this study support the established observation that tuberculous pleural effusions are predominantly lymphocytic exudates associated with elevated ADA activity. The biological basis for this association lies in the intense T-lymphocyte-mediated immune response that characterizes tuberculous pleuritis. Activated lymphocytes and monocytes release increased amounts of ADA, resulting in significantly higher enzyme activity within the pleural fluid. Similar observations have been reported by Valdés et al., Greco et al., and Liang et al., who demonstrated high diagnostic sensitivity and specificity of ADA for tuberculous pleural effusion.

The cytological examination in the present study provided important complementary information. Lymphocyte predominance was observed predominantly in tuberculous effusions, whereas neutrophilic predominance was more commonly associated with acute inflammatory or parapneumonic processes. In addition, identification of atypical or malignant cells allowed recognition of malignant pleural effusions, highlighting the continued importance of routine cytomorphological

evaluation. These observations are consistent with reports by Kumar et al. and Singh et al., who emphasized that cytology remains indispensable for the diagnosis of malignant pleural effusion even when biochemical markers are available.

One of the important strengths of the present study is the correlation between ADA activity and pleural fluid cellular profile. Studies by Burgess et al. and Aggarwal et al. have shown that the combination of elevated ADA levels and lymphocyte predominance substantially improves diagnostic specificity for tuberculosis compared with either parameter alone. The present findings support this concept and suggest that integrated interpretation of cytology and ADA is more clinically useful than isolated assessment of a single laboratory parameter.

Another clinically relevant observation is the practical utility of ADA estimation in resource-limited settings. Advanced molecular investigations such as PCR and GeneXpert provide microbiological confirmation but may not be universally available because of cost and infrastructure requirements. In contrast, ADA estimation is inexpensive, rapid, and technically straightforward. This makes it particularly valuable in tertiary care centers and peripheral laboratories serving populations with a high burden of tuberculosis. Similar conclusions have been reported in multiple Indian studies, including those by Sharma et al., Gupta et al., and Bhadade et al.

Despite its high diagnostic performance, ADA is not entirely disease-specific. Elevated ADA levels may occasionally be encountered in empyema, rheumatoid pleuritis, lymphoma, and certain malignant effusions. Therefore, ADA values should always be interpreted in conjunction with clinical findings, imaging studies, and cytological examination. The present study reinforces this principle by demonstrating that combined evaluation reduces the likelihood of diagnostic error.

The overall findings indicate that pleural fluid cytology and ADA estimation are complementary investigations rather than competing tests. Cytology provides morphological evidence of the underlying pathological process, while ADA reflects the immunological activity associated with tuberculous pleuritis. Together, they offer a rapid, economical, and reliable approach for the evaluation of pleural effusion in routine clinical practice.

In summary, the present study adds to the growing body of evidence supporting the combined use of pleural fluid cytological examination and ADA estimation for the diagnosis of tuberculous pleural effusion. This integrated approach is especially relevant in tuberculosis-endemic regions where timely diagnosis and initiation of therapy remain major public health priorities.

LIMITATIONS

This was a single-centre study with a relatively modest sample size of 100 patients, which may limit generalizability. Confirmatory molecular testing (PCR/GeneXpert) was not performed in all cases, and long-term clinical follow-up of patients was not undertaken.

CONCLUSION

The present study demonstrates that tuberculosis remains the leading cause of pleural effusion in this population, and that tuberculous pleural effusions are characteristically lymphocyte-predominant exudates with significantly elevated ADA activity. Combined evaluation of pleural fluid cytology and ADA estimation, at a cut-off value of 40 U/L, provides a rapid, cost-effective, and reliable diagnostic approach for differentiating tuberculous from non-tuberculous pleural effusion, and merits routine incorporation into the diagnostic work-up of pleural effusion, particularly in tuberculosis-endemic and resource-limited settings.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Nil.

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